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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 10/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/733,865	Applicant(s) SCHRAA ET AL.	
	Examiner Q. Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-10 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 7-10, and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-3, 5, 7-10, and 13 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 4, 6, 11, 12, 14-26 have been canceled. Claims 27-37 are newly submitted. Election was made **without** traverse in Paper No. 9.

Claims 1-3, 5, 7-10, 13, and 27-37 are pending and under current examination.

Drawings

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Objections

Claim 10 is objected to because a noun is missing (e.g. composition) after "pharmaceutical" in line 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9, 30, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivery of a gene of interest into a *tumor* cell comprising first administering intravenously to a host an *adenoviral vector* lacking said gene of interest, allowing for a neutralizing humoral response to be raised by the host, then *intratumoral* administering a second adenoviral vector comprising said gene of interest, does not reasonably provide enablement for delivery of a gene of interest to *any* recipient cell, using *any* type of vector, via *any* route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims recite a method for delivering a gene of interest and for minimizing liver toxicity of a gene delivery composition in a host comprising first delivering the vehicle lacking said gene of interest, allowing for neutralizing humoral response to be raised, and administering a greater amount of second delivery vehicle comprising the gene of interest. The specification teaches that adenoviruses are particularly useful for the development of gene-transfer vectors for human gene therapy (paragraph 0014) but limited by virus mediated cellular toxicity, i.e. the host anti-adenovirus immunity (paragraph 0016). In view of such, the invention provides a method of reducing the risk associated with administering adenoviral particles to subjects undergoing gene therapy (0026). In one aspect of the method, the subject is provided with the neutralizing antibodies by administering, to the subject, adenovirus of the same type as the

recombinant adenovirus to be administered, at a time before the administration of said recombinant adenovirus, to induce in the subject an immune response (0028).

With regard to the nature and the breadth of the claims, given the broadest reasonable interpretation that is consistent with the specification, the claims clearly or implicitly state the intended use of the method for reducing the risk of cytotoxicity associated with recombinant adenovirus mediated gene therapy, particularly reducing adenovirus mediated liver toxicity; and the claims embrace using any type of vectors (vehicles), via any route of administration, and targeting any recipient cell, therefore, the claims will be evaluated by that standard.

In view of the guidance provided, the specification teaches the first step as pre-vaccination, using "empty virus", and a dosage sufficient to elicit an immune response but insufficient to cause hepatotoxicity (0049, 0050); the working examples teach a hepatic artery infusion model and a pilot study determining the adv dosage according to liver toxicity. With regard to the preferred embodiment, the specification teaches (0074-0077), intravenous injection of 10^8 empty virus on the day of tumor inoculation (day 0), a boosting dose on day 13, and on day 18, adv.luciferase was administered at different doses (10^9, 10^8, and 10^7 IU), "*we observed gene transfer inhibition to the liver and spleen of the immune rates. High titers of neutralizing antibodies did not prevent luciferase expression in the tumor (fig. 1)*". In view of such, it appears that the specification fails to provide an enabling disclosure because the teachings of the specification do not support what is now claimed.

For example, the claims embrace delivering a gene of interest to any recipient cell, but the specification teaches that *gene transfer to the liver and spleen of the immune rats was inhibited.* (0077). It is only in the tumor, by intratumor injection, the levels of the transgene were minimally affected compared to un-immunized naïve rats. The specification teaches away from what is claimed.

The claims embrace any gene delivery vehicle, however, the only gene delivery vehicle discussed in the specification is the adenoviral vector. It is unclear whether such vigorous immunizing regimen is suitable for other vector systems, such as retroviral vectors, and herpes viral vectors, which is known for its immunogeneicity and cytotoxicity (*Robbins et al*, Pharmacol Ther 1998;80:35-47, entire article, section 2.3 particularly).

The claims embrace using a dose of the second vector having the gene of interest, greater than an amount, which can be neutralized by said humoral response. However, the specification fails to teach how to determine the dose for the second vector that is greater than the neutralizing antibody or a single example to illustrate such a dose that meets the claim limitation. Although the specification teaches delivering different doses as listed in paragraph 0075, and one of the second dose is greater than the empty vector (10^9), it is unclear the results from such administration regimen, whether the dose at 10^9 is considered sufficient amount which can be neutralized by said humoral response, and whether it is superior than a dose at 10^8, and 10^7 IU. Such teaching is important in view of what is known in the art at the time the instant application was filed. For example, *Harvey et al* (J Virol 1999 Aug;8:6729-42) teach, "IN

HUMANS, THE EXTENT OF THE RESPONSE IS DICTATED BY PREEXISTING ANTIBODY TITERS AND MODIFIED BY ROUTE OF ADMINISTRATION BUT IS NOT DOSE DEPENDENT" (abstract). The art of record teaches away from the instant claims.

The claims are further drawn to delivery the vector to any recipient cell via any route of administration, thus, concerning issues of vector targeting *in vivo.* While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Miller* (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). *Deonarain* reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). *Verma* (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been

achieved in the art (see entire article). *Verma* also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Concerning the adenoviral vector delivery, *Harvey et al* (J Virol 1999 Aug;8:6729-42) teach that humoral response to Ad vectors varies depending on the route of administration (see particularly the discussion section).

Concerning circumventing pre-existing immunity for repeated adenoviral vector administration in gene therapy, the art of record teaches away from the instant claims. *Parks et al* (Gene Ther 1999 Sept;6:1565-73) teach that mice immunized with hdAd2 produced Ad2-neutralizing antibodies which do not cross-react with the Ad5 virus; to determine if successful repeat Ad vector administration could be achieved by sequential use of alternative Ad serotypes, they injected mice with the *same* or different serotype vectors, and concluded that the sequential use of alternative serotypes, but not the same serotype, would prevent a decrease in transgene expression (see abstract). The teachings of *Kass-Eisler* (Gene Ther 1996;3:154-620), *Mack* (Human Gene Ther 1997;8:99-109), and *Mastrangeli et al* (Human Gene Ther 1996;7:79-87), are all drawn to the similar conclusion. Thus, it is evident that at the time of the invention, it is known in the art that the host immunity to adnenoviral vectors is a barrier for successful gene therapy, and the art-known strategy is to use an alternative serotype for circumventing the anti-adv neutralizing immunity and such could not be achieved using the vectors derived from the same serotype. The instant specification provides a new concept that is contrary to the existing one; thus, it is incumbent upon applicants to provide sufficient

and enabling teachings within the specification for such therapeutic regimen. However, the specification fails to provide such an enabling disclosure to support the scope of the claims as analyzed in detail in the proceeding paragraphs.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require undue experimentation to practice the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5, 7-10, 13, and 27-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, "essentially identical". The specification does not define the term, it is unclear what structural components are included and excluded from the claim recitation, thus, the metes and bounds of the claims are unclear.

Claims 3, 27, 29, and 32 are vague and indefinite because claims 3 and 27 are drawn to timing of the vector administration, which would further limit a method claim. However, claims 3 and 27 are depend from a composition claim wherein the timing of administration would not describe the nature or the characteristics of the composition. It is unclear whether the applicants intend to claim a composition or a method.

The claims are vague and indefinite because of the claim recitation, "said first gene delivery vehicle and said second gene delivery vehicle being cross-reactive". It is unclear how the two vehicles considered being cross-reactive, thus, the metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 5, 7-10, 13, 27-30, 34, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by *Bramson et al* (Gene Ther 1997;4:1069-76, IDS).

Claims 1, 2, 5, and 28 are drawn to a kit of parts comprising a first gene delivery vehicle comprising a nucleic acid comprising a gene to be delivered to a recipient cell, and a second gene delivery vehicle essentially identical to said first gene delivery vehicle, but lacking said gene to be delivered, wherein the vehicles are of adenoviral origin. Claims 7-9, 30, 34, 36 are drawn to a method for delivering a gene of interest and for minimizing liver toxicity in a host of a gene delivery composition comprising first delivering the vehicle lacking said gene of interest, allowing for neutralizing humoral response to be raised, preferably more than 14 days, and administering a greater amount of second delivery vehicle comprising the gene of interest. Claim 10 is drawn to

a method comprising providing the kit of parts together with a pharmaceutically acceptable carrier.

Bramson et al teach a gene delivery system comprising a wild-type adenovirus 5 (Ad5), and a recombinant Ad5 encoding for IL-12 as gene of interest (AdmIL12). The vectors are in a pharmaceutically acceptable carrier when delivered to a subject. *Bramson et al* go on to teach first intranasal administering 10^8 of Ad5, and 31 days later, administering $5X10^8$ AdmIL12 intratumorally. They further teach that even though the Ad5 immunization cause high levels of circulating neutralizing antibodies to adenovirus, the treatment still induce tumor regression effectively (left column, page 1070), and concluded that pre-immunity to Ad did not reduce the efficacy of the AdIL12 treatment of tumors. They further teach that the preimmunity has an inhibitory effect preventing adenovirus from dissemination to other organs, particularly a dramatic inhibition for liver dissemination, therefore, a beneficial effect of inhibiting the dissemination of virus from the site of injection and protecting peripheral tissue from any adverse effects of gene transfer. Therefore, *Bramson et al* anticipate the instant claims.

Claims 1, 2, 5, 10, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by *Song et al* (Hum Gene Ther 1997;8:1207-17).

Claims 1, 2, 5, and 28 are drawn to a kit of parts comprising a first gene delivery vehicle comprising a nucleic acid comprising a gene to be delivered to a recipient cell, and a second gene delivery vehicle essentially identical to said first gene delivery vehicle, but lacking said gene to be delivered, wherein the vehicles are of adenoviral

origin. Claim 10 is drawn to a method comprising providing the kit of parts together with a pharmaceutically acceptable carrier.

Song et al teach a gene delivery system comprising at least two replication-deficient adenovirus; one comprises the gene to be delivered (Ad.CAT or Ad.beta-gal), and the other identical to AdCAT construct but lacking the gene to be delivered (Ad.Null). The vectors are in a pharmaceutically acceptable carrier when delivered to a subject. Therefore, *Song et al* anticipate the instant claims.

Claims 1, 2, 5, 10, 13, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by *Russi et al* (Hum Gene Ther 1997;8:323-30).

Claim 13 is further drawn to interleukin as a gene to be delivered to a recipient cell.

Russi et al teach a gene delivery system comprising at least two replication-deficient adenovirus, one comprises interleukin-2 coding region as the gene to be delivered (AdCMV.IL-2), and another identical in construct but lacking the gene to be delivered (AdCMV.Null). The vectors are in a pharmaceutically acceptable carrier when delivered to a subject. Because the system of *Russi et al* comprises the two vectors, it meets claim limitation. Therefore, *Russi et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Russi et al* (Hum Gene Ther 1997;8:323-30), in view of *Esandi et al* (Gene Ther 1998;5:778-88).

Claims 1, 2, 5, 31, and 33 are drawn to a kit of parts comprising a first gene delivery vehicle comprising a nucleic acid comprising a gene to be delivered to a recipient cell, and a second gene delivery vehicle essentially identical to said first gene delivery vehicle, but lacking said gene to be delivered, wherein the vehicles are of adenoviral origin, wherein the gene to be delivered is IL-3.

Russi et al teach a gene delivery system comprising at least two replication-deficient adenovirus, one comprises the gene to be delivered (AdCMV.IL-2), and another identical in construct but without the gene to be delivered (AdCMV.Null). *Russi et al* do not teach delivering IL-3 as the gene of interest.

Esandi et al teach using an adenoviral vector encoding IL-3 in gene therapy for non-small cell lung cancer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Russi et al,* by simply substituting IL-2 with IL-3 as taught by *Esandi et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention with the gene of interest for a particular need of therapy. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bramson et al* (Gene Ther 1997;4:1069-76, IDS), in view of *Esandi et al* (Gene Ther 1998;5:778-88).

Bramson et al teach a gene delivery system comprising a wild-type adenovirus 5 (Ad5), and a recombinant Ad5 encoding for IL-12 as gene of interest (AdmIL12). *Bramson et al* go on to teach first intranasal administering 10^8 of Ad5, and 31 days later, administering $5X10^8$ AdmIL12 intratumorally. They further teach that even though the Ad5 immunization cause high levels of circulating neutralizing antibodies to adenovirus. *Bramson et al* do not teach a vector encoding an IL-3.

Esandi et al teach using an adenoviral vector encoding IL-3 in gene therapy for non-small cell lung cancer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Bramson et al,* by simply substituting IL-12 with IL-3 as taught by *Esandi et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention with the gene of interest for a particular need of therapy. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
October 18, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER